TECHNICAL ABSTRACT

A phase II, open-label, ascending-dose study of the safety and efficacy of Trinam™ (EG004) in stenosis prevention at the graft-vein anastomosis site in dialysis patients - Protocol 102

Hemodialysis access complications remain a major cause of morbidity for patients with end-stage renal disease who are undergoing chronic hemodialysis. Vascular access complications occur in approximately 40% of patients with polytetrafluorethylene (PTFE) grafts within the first 6 months, primarily due to stenosis and thrombosis. Thrombosis at the site of vascular access increases the risk of infection and the need for hospitalization, and may lead to loss of potential new sites for vascular access. To a large extent, the failure of hemodialysis access is due to the rapid development of an intimal hyperplastic lesion in the region of anastomosis between the PTFE graft and the vein. The hospital costs related to hemodialysis access procedures are estimated to be around $1.3 billion per year and the total cost of hemodialysis complications to the US healthcare system is thought to be in excess of $2 billion per year.

Ark Therapeutics Ltd is developing a vascular endothelial growth factor D (VEGF-D) gene in an adenoviral vector which is delivered locally to the adventitial surface of a graft-vein anastomosis by means of a collagen collar device. The proposed indication for this product (Trinam™), is the prevention of intimal hyperplasia at the graft-vein anastomosis site in patients who require vascular access to facilitate hemodialysis for end-stage renal disease.

The rationale for Trinam to prevent intimal hyperplasia at the graft-vein anastomosis follows the discovery that VEGF has a “vasculoprotective” action, resulting in inhibition of smooth muscle cell migration and proliferation (1). The fundamental mechanism for this vasculoprotective effect of VEGF, as distinct from its more widely appreciated `angiogenic' role, is that VEGF acts on surface receptors on endothelial cells resulting in increased production of nitric oxide and prostacyclin. These entities diffuse into the media of the blood vessel wall and counter the tendency for intimal hyperplasia to develop. In an *in vivo* rabbit model of intimal thickening in carotid arteries, adventitial delivery of VEGF using a silastic collar as a gene delivery reservoir prevented smooth muscle cell proliferation without evidence of new blood vessel formation, indicating that the mechanism by which VEGF inhibited intimal hyperplasia did not involve angiogenesis (2).

The objective of the proposed study is to assess the efficacy and safety of local delivery of Trinam when applied to the graft-vein anastomosis site in patients with end-stage renal disease who require vascular access for hemodialysis. The study is a dose-escalation study, with the first cohort of eight patients to receive a dose of Trinam at 4×10^9 viral particles (replication-deficient adenoviral vector) at the time of surgical placement of a

PTFE arm graft. There will be an independent safety review conducted after these eight patients are treated. Assuming a satisfactory safety review, a second cohort of eight patients will be treated with Trinam at 4 x 10^{10} viral particles. In addition, four patients will be recruited to the study as controls, and will undergo the standard graft placement but will receive no treatment. It is hypothesised that Trinam administration will result in less stenosis at the graft-vein anastomosis site (as measured by fistulography) compared with controls and therefore will reduce the need for interventions in dialysis patients. All patients will be evaluated over 12 months. The highest dose of Trinam that might be administered in this study was not associated with any significant toxicology findings in a preclinical study of pigs in which a PTFE loop-graft was anastomosed from the carotid artery to the internal jugular vein to mimic hemodialysis vascular access surgery.

References:

1. Zachary I, Mathur A, Yla-Herttuala S. Vascular protection. A novel nonangiogenic cardiovascular role for vascular endothelial growth factor. *Arterioscler Thromb Vasc Biol* 2000;**20**:1512-1520.

2. Laitinen M, Zachary I, Breier G, et al. VEGF gene transfer reduces intimal thickening via increased production of nitric oxide in carotid arteries. *Hum Gen Ther* 1997;**8**:1737-1744.